Fiber Treating Metabolic Syndrome

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Abstract

The number of individuals diagnosed with metabolic syndrome has risen dramatically in recent years. Although not a disease itself, metabolic syndrome significantly raises the risk of developing cardiovascular disease and type 2 diabetes mellitus, both considered to be epidemics. Therefore, it is critical to promote aggressive therapies that effectively combat conditions associated with the metabolic syndrome. However, treating metabolic syndrome is complicated due to the complex nature of its pathophysiology coinciding with the many health abnormalities metabolic syndrome is often associated with, including but not limited to, insulin resistance, central obesity, hypertension, and atherogenic dyslipidemia. One promising compound that has been demonstrated to alleviate metabolic syndrome is fiber. The various types of fiber work through multiple mechanisms of action in the human body and can potentially result in weight loss in addition to blood glucose control and the lowering of cholesterol. Therefore, increasing intake of dietary fiber might prevent or even reverse some of the negative health anomalies associated with metabolic syndrome. The purpose of this review is to provide a cursory overview of the core components of metabolic syndrome and address how fiber intake may combat these conditions.

Keywords: Cardiovascular disease; Central obesity; Insulin resistance; Resistant starch; Type 2 diabetes mellitus

Introduction

It has been established that patients diagnosed with metabolic syndrome (MS) have significantly greater incidence of developing type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) [1-3]. Indeed, diabetes is a nationwide epidemic in the United States affecting nearly 26 million Americans, with 90-95% of these cases being T2DM [4]. The monetary costs for diabetes alone accounts for an estimated 245 billion dollars in the United States annually [5]. CVD is the primary cause of death in people with T2DM [6,7] and ranks number one in fatalities worldwide [8]. Similar to increased incidences of individuals with T2DM, diagnosis of people with MS is steadily rising [9].

It has been proposed that fiber may assist in the regulation of abnormalities that are commonly linked with MS [10-13]. Dietary fiber is capable of a diverse array of positive health effects due to different mechanisms of action in various types of fibers. Ingestion of fiber may have a pronounced effect on combating MS, both directly and indirectly, via influencing physiological pathways that deal with nutrient uptake, energy balance, appetite, satiety, and waste excretion. The purpose of this review is to provide an understanding of the health conditions and risks linked to MS and how dietary fiber may prevent or even reverse some of the health abnormalities associated with MS.

Metabolic Syndrome

While MS is considered to be a relatively new concept, there have traditionally been four main conditions associated with MS; insulin resistance (IR), obesity, hypertension, and dyslipidemia [14]. However, the International Diabetes Federation offered a novel proposition characterizing MS [15,16]. The International Diabetes Federation deemed central obesity (CO) and atherogenic dyslipidemia as core components for the diagnosis of MS and used them to replace obesity and dyslipidemia, respectively [15]. Furthermore, the waist circumference values to diagnose CO for the International Diabetes Federation are race and ethnic specific, which innovatively established unique diagnostic criteria. The International Diabetes Federation also emphasized the important relationship of proinflammatory and prothrombotic states to MS [15]. Though difficult to discern, prothrombosis and systemic inflammation are serious consequences of MS. It has been noted that both CVD and T2DM are considered to be inflammatory diseases [17, 18] and it is recognized that most cardiovascular events are caused by a thrombus [19]. The latest consensus among MS experts is that proinflammatory and prothromtotic states are prevalent in individuals having metabolic risk factors for MS [20]. It is also important to mention that no single risk factor appears to be most important in terms of mortality [21]. Thus, understanding the pathophysiology of all components plus best ways to treat these conditions and MS as a whole is crucial.

Central Obesity

The International Diabetes Federation declares CO to be the only mandatory criteria for diagnosis of MS [16]. CO is excessive accumulation of visceral adipose tissue. This is often correlated with IR [21-23]. CO may be more detrimental to proper glucose metabolism as overweight or even obese people with proportional body fat do not always show signs of IR [24], while in some cases normal weight individuals with excessive visceral adiposity may display IR [25].

Compared with subcutaneous adipose tissue, visceral adipose tissue is a more active tissue in two distinct ways. First, visceral adipose tissue is more metabolically active than subcutaneous adipose tissue due to increased adrenergic activity as visceral fat has more beta adrenergic receptors and is more sensitive to lipolytic catecholamine effects compared with subcutaneous fat [26-30]. Excess visceral adipose tissue triggers an abundant release of free fatty acids (FFA) that spill into the hepatic portal vein, quickly making their way to the liver and exacerbating IR [31]. Marked increases in FFA elevate triglycerides in

the body [32,33], which are one of the main features of atherogenic dyslipidemia [15]. Increases in FFA also reduce insulin clearance [31,34] which is a strong indicator of IR [34]. Second, visceral adipose tissue is more hormonally active compared to subcutaneous adipose tissue. Visceral adipose tissue initiates key inflammatory proteins, namely interleukin-6, tumor necrosis factor alpha, and C-reactive protein, all of which have been linked or associated with IR [35-38].

Insulin Resistance

IR can be simply stated as, "a state where there is a reduced biologic effect for any given concentration of insulin" [39]. IR is believed to be a key player in triggering MS pathogenesis [40]. IR appears to originate from a weakened response to insulin in glucose-responsive cells [41]. More specifically, hyperinsulinemia occurs postprandially when glucose cannot be sufficiently cleared from the bloodstream by myocytes, resulting in de novo lipogenesis and atherogenic dyslipidemia [42]. Hyperinsulinemia causes a subsequent downregulation of insulin receptors, impairing insulin function [43,44]. Consequently, constant long-term hyperinsulinemia intensifies IR and plays a direct role in the development of T2DM [45,46].

Atherogenic Dyslipidemia

Atherogenic dyslipidemia is a critical factor in developing CVD related to MS. While atherogenic dyslipidemia plays a prominent role in the development of atherosclerosis, endothelial dysfunction works alongside atherogenic dyslipidemia to contribute to the development of CVD [47], as endothelial dysfunction also promotes atherosclerotic plaque development [48,49]. This effect may provide to be synergistic in patients with MS, as endothelial dysfunction is predominantly found in this population [50]. Other modes of action exist in MS which directly influence atherogenic dyslipidemia. Elevated FFA, commonly observed as a result from IR, accumulate in the liver causing a high FFA flux. This can result in increased production of very low density lipoproteins, triglycerides, apolipoprotein B, and a reduction in high density lipoproteins [31]. High triglycerides and apolipoprotein B along with low levels of high density lipoproteins are known to be atherogenic [51] and their respective concentrations are used to determine atherogenic dyslipidemia [15].

The negative effects of atherogenic dyslipidemia can be manipulated by hormonal factors. As mentioned earlier, the adipokines interleukin-6 and tumor necrosis factor alpha can be generated from visceral adipose tissue [35-38]. Tumor necrosis factor alpha and interleukin-6 inhibit the secretion of adiponectin, an adipokine that displays anti-atherogenic effects [52,53]. Anti-atherogenic capabilities of adiponectin include inhibition of monocytes attaching to endothelial walls, resulting in down regulation of scavenger receptors which prevents foam cells from changing into macrophages [54]. This lack of protection may increase the susceptibility of atherosclerotic plaque to develop from atherogenic dyslipidemia present in individuals suffering from MS.

Hypertension

Hypertension associated with MS may originate from several participating factors. These factors may include the degree of sympathetic activity within the central nervous system, adjustments in salt sensitivity and management in the kidneys, endothelin-1 mediated vasoconstriction, and angiotensin II [55]. Moreover, increases in FFA have been shown to impair vascular reactivity in humans [56] which is detrimental to sustaining normal blood pressure. CO has also been considered to influence hypertension, being an even stronger risk factor than general obesity [57]. Visceral adipose tissue secretes more angiotensinogen than subcutaneous fat [58,59] which may increase blood pressure via altering the renin-angiotensin system through increasing this system's main substrate (angiotensinogen) resulting in vasoconstriction.

Normal insulin signaling is critical in maintaining normal blood pressure and alterations in insulin signaling may result in hypertension [57]. Insulin is known to increase the release of nitric oxide which causes vasodilatation [60]. The end result of this is a potential drop in blood pressure. However, as seen with IR, disturbances to the endothelium may evolve which might prevent an insulin induced-nitric oxide vasodilatation effect [61], possibly resulting in hypertension. The consequences of both IR and hypertension is thought to be particularly detrimental to health and markedly increases the chance of developing CVD compared to just suffering from one of these ailments [62].

Systemic Inflammation

There appears to be a strong relationship between MS and inflammation [63]. The type of inflammation commonly seen in patients suffering from MS is a chronic, low-grade inflammation coined systemic inflammation. Indeed, adipocytes are able to produce adipokines that may lead to a proinflammatory state [64]. Many different adipokines are quite capable of producing systemic inflammation. However, the adipokines interleukin-6, C-reactive protein, and tumor necrosis factor alpha in particular show extensive systemic inflammation exacerbation, as these adipokines are also cytokines with acute phase and/or immune responses as their underlying purpose/operation in the body. Interleukin-6 can initiate systemic inflammation on its own as well as intensify systemic inflammation by augmenting secretion of interleukin-1 and tumor necrosis factor alpha [65]. High levels of C-reactive protein have been linked to T2DM and CVD in addition to being a strong marker for systemic inflammation [66]. Though it has been suggested that IR amplifies the state of proinflammation with systemic inflammation as the end outcome [31, 55], there are also hypotheses supporting the notion that IR can result from systemic inflammation [67,68].

Prothrombosis

A recent concern of MS is the relationship with prothrombosis and increased CVD risk. In a prothrombotic state, a dangerous clot can form if a vulnerable plaque ruptures [69]. Fibrinolysis impairment may cause vascular damage and initiate obstructions of the circulatory system inherently increasing CVD risk [70-75]. Prothrombosis in people with MS may be due to the negative synergy associated to smaller amounts of tissue plasminogen activator secreted in correlation with higher concentrations of the adipokine plasminogen activator inhibitor-1 being secreted from the outcome of insulin resistance and glucose intolerance [70-73,75]. The enzyme tissue plasminogen activator catalyzes the conversion of plasminogen to plasmin, an enzyme essential to fibrinolysis, while plasminogen activator inhibitor-1 is the primary inhibitor of tissue plasminogen activator. If plasminogen activator inhibitor-1 and tissue plasminogen activator levels attributed to prothrombosis remain unchanged, repeated bouts of unwanted coagulation may ensue, which when combined with atherosclerosis [70-76], increases the chance of a cardiovascular event. While prothrombosis is a major risk factor for CVD, as a thrombus is virtually considered a requisite for the most fatal type of CVD (i.e. myocardial infarction), prothrombotic states shouldn't raise incidence for T2DM. Other conditions of MS though, such as CO, IR, and systemic inflammation, increase the risk of both CVD and T2DM. Nevertheless, all conditions of MS should be taken seriously and attempted to be alleviated as they are thought to work in synergistic fashion to markedly increase incidence of T2DM and/or CVD.

Fiber

Dietary fiber comes from a variety of food sources, in particular fruits, vegetables, legumes, nuts, and whole grains. A common method of grouping fiber types is determining their solubility in water. Soluble fibers dissolve in water while insoluble fibers do not [77]. An approximate ratio for many fibrous foods is 2/3 of insoluble fiber to every 1/3 of soluble fiber [78]. The third type of fiber, named Resistant Starch (RS), comprises of either starch and/or products resulting from starch digestion in humans bypassing digestion that would normally occur in the small intestine consequently entering the large bowel [79]. It should be noted RS only comes from starch that is not fully digested [80].

Reputable health organizations have recognized fiber as an invaluable nutrient. Both the World Health Organization and World Cancer Research Fund have emphasized that dietary fiber can help prevent obesity and weight gain [81,82]. Additionally, a joint consultation on human nutrition by the Food and Agriculture Organization of the United Nations and World Health Organization previously explained that a significant advance in realizing key vital health attributes of carbohydrates in the past twenty years has been due to discovering RS [83]. Furthermore, the National Academy of Sciences Food and Nutrition Board acknowledged RS as a beneficial carbohydrate [84].

Substantial evidence indicates fiber may contain numerous factors which promote many distinct health benefits [85]. Moreover, it appears that fiber consumption and markers of metabolic syndrome are inversely correlated with one another [86]. Additionally, it has been acknowledged that over 90% of the adult population fails to meet adequate intake recommendations for fiber [87]. Therefore, increasing fiber intake may prove to be beneficial for the vast majority of adults suffering from MS.

Appetite Control, Satiety and Positive Body Composition Change

Dietary fiber may provide satiety [88,89] resulting in a decreased caloric intake and improved weight loss. Achieving weight loss through a hypocaloric has shown to effectively combat metabolic syndrome by reducing central obesity, blood pressure, fasting glucose and insulin, triglycerides, C-reactive protein, low density lipoproteins, and increasing high density lipoproteins and insulin sensitivity [90]. Soluble fibers capable of holding large volumes of water and able to create viscous gels within the gastrointestinal tract have shown to temporary suspend gastric emptying into the duodenum, slowing down digestion and providing a longer duration of satiety after meals [91,92].

Insoluble fibers can control appetite by acting as a powerful bulking agent. Insoluble fibers are extremely resilient to fermentation by bacteria inside the colon [93] which may increase fecal matter both directly and indirectly. Insoluble fibers which are excreted through the colon may take-up other fermentable carbohydrates with them as well, allowing them to pass the fermentation process and be excreted as waste instead [93]. This bulking effect in turn significantly increases gastrointestinal load which may promote satiety and create a feeling of fullness. Research has also shown insoluble fiber assists in reducing overall caloric consumption shortly after meals [94] as well as promoting weight loss [95,96].

RS starch may also promote satiety and curb hunger. A study analyzed rodent brains to evaluate possible changes when being fed either a high RS diet or a low RS diet [97]. Rodents fed the high RS diet displayed a state similar to a satiated animal in hypothalamic regions of the brain while the low RS diet showed a fasted state instead, suggesting RS as a factor in controlling hunger [97].

Increasing fiber intake may also have a profound impact on positively influencing body composition changes, too. Positive changes in body composition may aid in the prevention or treatment of metabolic syndrome as increased skeletal muscle mass may have protective qualities against MS [98]. Rodents fed a low or high RS chow had substantial differences in body composition, favoring the anti-obesity effects of high RS intake [97,99]. While mean body weights were comparable among both groups, lean body mass was higher in the high RS group. The high RS group also exhibited lowers visceral, subcutaneous, and intra hepatocellular fat content when compared to the low RS group [97,99]. The lower visceral fat level observed in these studies is of utmost importance regarding MS since excessive visceral fat causes CO. Thus, possibly changing body composition through decreasing visceral adipose tissue by consuming RS may treat CO. By reducing CO through the ingestion of RS, other conditions of MS may be alleviated as well, such as IR and systemic inflammation, which may effectively combat MS.

Glycemic Control

Dietary fiber has been shown to effectively regulate both IR and T2DM [100]. Fiber has the unique ability to adsorb certain molecules within the gastrointestinal tract. Enzymes involved with carbohydrate digestion may be affected by viscous fibers creating a wall that hinders their action as a catalyst [101]. Fiber viscosity is particularly important by temporarily suspending glucose assimilation, slowing transfer time, lowering blood glucose concentrations, and having a positive influence upon hormone responses, such as insulin and glucagon-like peptide 1, ultimately influencing nutrient uptake [102-105]. In addition to these unique features, data from epidemiological studies discovered a inverse correlation with insoluble fiber intake and developing T2DM [106,107].

RS can lengthen time duration of glucose entering the bloodstream, which has a potent, direct effect on regulating blood glucose. RS slows the rate at which glucose reaches the blood which has been observed *in vitro* [108] and *in vivo* in humans [109]. Prolonging glucose into the bloodstream may act synergistically by positively influencing body composition and satiety by causing less insulin to be secreted and increasing the likelihood of lipolysis in addition to controlling hunger and maintaining normal body weight [110,111]. This has been previously substantiated from clinical research performed comparing two similar foods originating from potato starch [112, 113]. In these studies, one type of potato starch was raw and contained RS but the other type of potato starch was pre-gelatinized and did not contain any RS. The RS group from the first study resulted in significantly lower blood insulin levels plus better postprandial satiety than their non-RS counterparts [112]. Lipolysis was also demonstrated to be higher in the RS group compared to the non-RS group [113], which may indicate a shift in fatty acids utilized as an efficient energy source instead of used for triglyceride synthesis and storage.

RS may also assist in blood glucose regulation through preventing IR via manipulating fat location and adipocyte size in the body. In two rodent studies previously mentioned [97,99], a ratio of insulin to glucose was higher in the low RS group compared to their high RS counterparts, suggesting an IR state. It was also noted that the low RS set had significantly higher levels of intrahepatocellular fat [97,99]. It may be plausible to assume that the higher intrahepatocellular fat content may have initiated IR displayed in these studies. Surmounting evidence has observed positive correlations between intrahepatocellular fat and IR, with speculation that hepatic steatosis may play a chief role in the

pathogenesis of IR [114,115]. Additionally, since larger adipocyte size is known to reduce insulin sensitivity [116], this may partially attribute to the insulin resistant states observed, as the low RS diet resulted in a considerably larger adipocyte size in comparison to rats fed a high RS diet [97]. Thus, it may be possible for a type of synergistic ability to occur through the consumption of various fibers resulting in decreasing adipocyte size, hepatic steatosis, and blood glucose concentrations, ultimately improving IR and preventing the progression of T2DM.

Atherogenic Dyslipidemia Treatment & Cardiovascular Disease Prevention

Positive lipid alterations known to lessen the chance of CVD have been observed with fiber consumption [117]. Soluble fibers as well as the insoluble fibers such as lignin and specific types of chitosan are capable of adsorbing bile acids, fatty acids, and cholesterol, with these fiber attached molecules likely passing the small intestine and the end result being broken down by bacteria inside the large intestine or simply excreted with feces, resulting in less overall cholesterol and bile acids inside the body to be absorbed by the liver. Lowered levels of cholesterol within the liver may initiate low density lipoproteins (LDL) to be cleared from the blood. Inadequate amounts of bile acids absorbed by the liver triggers the production of new bile acids from the utilization of cholesterol. Both of these effects decrease serum cholesterol [118]. Short chain fatty acids (SCFA), byproducts of fiber fermentation in the colon has also been shown to lower cholesterol [119,120]. The mechanism of action, that SCFA decrease cholesterol is via reducing cholesterol synthesis rate [119]. Fiber also has the ability to influence the atherogenic dyslipidemia markers triglycerides and apolipoprotein B concentrations in the body as well. Evidence has indicated soluble fiber capable of lowering both triglyceride and apolipoprotein B levels [121]. Though the improvement of all conditions of MS is critical to health and well-being, treating atherogenic dyslipidemia and lessening the chance of CVD is of utmost importance in reducing mortality in patients suffering from MS, as not only is CVD more prevalent in individuals with MS but more people with MS die from CVD as well [122,123].

Final Remarks

Fiber has been previously recognized as a potential candidate to assist in treating MS [10-13]. An intake of a variety of fibers may be the most appropriate way of combating MS versus just increasing one class of dietary fiber. Diets high in fiber may also have therapeutic capabilities for alleviating certain MS amnolies similar to drug treatment. In particular, a fiber rich diet known as the dietary portfolio or portfolio diet, but colliquolly called the "Jenkins diet" has been shown to lower cholesterol as effectively as statin therapy in healthy adults suffering from hyperlipidemia [124]. Since increasing fiber intake may preclude medication, is non-invasive, and is only counterproductive at very high levels [125,126], it may be wise to consume a high fiber diet. Fiber from foods may be a better approach to obtaining daily fiber rather than from supplementation. Aside from the higher nutrient profile fiber rich foods display when compared to fiber supplements, it has been projected that increasing fiber consumption via consuming whole grains, fruits, vegetables, and legumes would significantly reduce obesity in industrialized nations [127].

Consumption of dietary fibers causes an array of different biochemical reactions in line with the kind of fiber being ingested. Therefore, this acknowledgment should be incorporated into treatment of MS as well. It is also imperative to recognize fibers that promote health benefits by decreasing T2DM and CVD risk, as these are the two diseases that are significantly increased in people who have MS [1-

3]. For example, whole grain intake is correlated with lowered risk of T2DM, heart disease, and stroke [128]. Evidence supports the notion that the lower whole grain consumption is in populations, the rate of incidence rises for individuals developing MS [129,130]. Whole grains are known to contain ample amounts of dietary fibers [131]. Whole grains may effectively alleviate MS by promoting satiety and weight loss primarily from the mid-section, improve blood glucose, lipid, and insulin levels, and lower blood pressure and inflammation [132-138].

In general, soluble fiber may be able to positively alter blood lipids [139]. Specific types of soluble fiber though may have an even more prominent effect on other conditions of metabolic syndrome, such as IR, hypertension, systemic inflammation, and oxidative stress [121,140] in addition to the benefits upon plasma cholesterol and triglyceride levels [121]. Cereal fiber is another type of fiber that appears very promising with the intent of preventing MS [130]. Cereal fiber intake coincides with decreasing the chance of developing T2DM [141-145] as well as lowering CVD risks [107]. Also, raising cereal fiber consumption in the diet enhances insulin sensitivity [146].

Future studies are needed to discover exactly which fibrous components display positive effects upon the treatment of MS, as well as the ones which may cause negative conditions. It has already been suggested that fiber may increase prothrombosis [147-150], but more recent literature contests this [151]. Unfortunately, data in pertinence to this topic is brief and anachronous in relation to MS. Future studies should try to determine whether fiber increases blood coagulation or not. Furthermore, investigations should be performed to understand both the direct and indirect mechanisms of action these fiber components have relating to the pathophysiology of MS. It certainly should not be ignored that a higher fiber diet may result in notable weight loss, which may also alleviate conditions of MS. Therefore, until clinical trials are conducted that actually demonstrate a causal inference regarding fiber preventing and/or treating MS independent of other factors (e.g. weight loss), caution should be exercised. If however certain components of fiber do indeed have a profound impact on alleviating certain conditions of MS, then extraction of these substances for medicinal and/or supplementation purposes may in fact be applied for use in the future of individuals suffering from MS. Nevertheless, if this were employed into modern practice one day, a high intake of whole grains, fruits, vegetables, nuts, seeds, and legumes would still be commended for the many numerous health benefits they provide other than their respected fiber contents.

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